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ENDOTHELIAL FUNCTION, SYSTEMIC INFLAMMATION AND CARDIAC HEMODYNAMICS IN DIFFERENT AGE PATIENTS WITH POST INFARCTION CHRONIC HEART FAILURE

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Abstract. Endothelial function, systemic inflammation and cardiac hemodynamics in different age patients with post infarction chronic heart failure. Zabida Abdunaser A.M. *Heart failure (HF) is a major cause of morbidity and mortality. After myocardial infarction, physiological and anatomical ventricular changes occur, There is also an inflammatory reaction with release of cytokines, growth factors and reactive oxygen species production, which contributes to perpetuate ventricular dysfunction. The study was designed to evaluate the level of inflammatory markers (white blood cells and C-reactive protein), endothelial function and cardiac hemodynamic in different age patients with post infarction heart failure. We divided 45 patients with HF with preserved ejection fraction (HFpEF) with mean age 67,5 [65,5; 71,7] years into two main groups. 1st group: 25 patients with HFpEF and history of myocardial infarction. 2nd group: 20 patients with HFpEF and stable angina (without myocardial infarction in anamnesis). Standard laboratory blood tests for erythrocyte sedimentation rate, C-reactive protein, haematological parameters, lipid profile, glucose, renal and liver function tests, echocardiographic examination, endothelial function estimation were performed. Patients with a history of myocardial infarction had significantly higher levels of left ventricle end diastolic volume, left ventricle end systolic dimension ($p<0.05$). There was estimated direct correlation between LVEDV, LVESD and age - $R=0.68$ ($p<0.05$), $R=0.52$ ($p<0.05$). Further analysis of cardiac hemodynamics depending on age revealed significant differences between LVEDV indices in patients with myocardial infarction. A significantly higher level of leukocytes was found in patients with HFpEF with a history of myocardial infarction in both groups ($p<0.05$). A direct correlation between the leukocyte count and age in patients with HFpEF-$R = 0.48$ ($p< 0.05$) was also found. Patients with HFpEF with a history of myocardial infarction had a significantly higher level of CRP, including in the age aspect ($p<0.05$). A direct correlation between CRP level and age was established in patients with HFpEF - $R=0.46$ ($p<0.05$). It was revealed that in the older age groups with myocardial infarction the signs of endothelial dysfunction were significantly more frequent ($p<0.05$). Reverse correlations were established between the level of endothelium dependent vasodilatation (ESVD) and CRP ($R=-0.48$, $p<0.05$), triglycerides ($R=-0.45$, $p<0.05$), diastolic blood pressure ($R=-0.54$, $p<0.05$). Conclusion: high level of inflammation markers, endothelial dysfunction and changes in cardiac hemodynamics were recorded more often in elderly patients with post infarction heart failure.*

Реферат. Ендотеліальна функція, системне запалення та серцева гемодинаміка в пацієнтів з хронічною серцевою недостатністю на тлі перенесеного інфаркту залежно від віку. Забіда Абдунасер А.М. *Серцева недостатність (СН) є провідною причиною захворюваності та смертності. Після інфаркту міокарда відбуваються фізіологічні та анатомічні зміни в шлуночках. Це супроводжується запальною реакцією з вивільненням цитокінів, факторів росту та утворення реактогенних форм кисню, що призводить до формування шлуночкової дисфункції. Мета дослідження – оцінити рівні маркерів запалення (числа лейкоцитів та С-реактивного протеїну (СРП)), функцію ендотелію та серцеву гемодинамку в пацієнтів з постінфарктною СН різних вікових груп. Ми розподілили 45 пацієнтів з СН зі збереженою фракцією викиду (ФВ) та медіаною віку 67,5 [65,5; 71,7] років на дві основні групи. Перша – 25 пацієнтів із СН зі збереженою фракцією викиду та інфарктом міокарда (ІМ). Друга – 20 пацієнтів із СН зі збереженою ФВ та стабільною стенокардією (без ІМ в анамнезі). Виконано стандартні лабораторні дослідження крові для визначення швидкості осідання еритроцитів, СРП, гематологічних параметрів, ліпідного профілю, глюкози, показників функції нирок та печінки, ехокардіографічне дослідження, визначення ендотеліальної функції. У пацієнтів з ШМ в анамнезі були достовірно вищі показники кінцевого діастолічного розміру (КДР) та кінцевого систолічного розміру (КСР)*

лівого шлуночка (ЛШ) (p<0,05). Встановлені достовірні кореляційні зв'язки між КДРЛШ, КСРЛШ та віком (R=0,68, p<0,05 та R=0,52, p<0,05). Подальший аналіз кардіальної гемодинаміки залежно від віку виявив достовірні відмінності між індексами КВРЛШ у пацієнтів з ІМ (p<0,05). Достовірно вищі рівні лейкоцитів були виявлені в пацієнтів з СН зі збереженою ФВ з ІМ в анамнезі (p<0,05). Прямі кореляційні зв'язки між числом лейкоцитів та віком були встановлені в пацієнтів з СН зі збереженою ФВ – R=0,46 (p< 0,05). Було виявлено, що в старших вікових групах з ІМ в анамнезі ознаки ендотеліальної дисфункції зустрічалися частіше (p<0,05). Встановлені зворотні кореляційні звязки між рівнем ендотелій залежної вазодилатації (ЕЗВД) та СРП (R=-0,48, p<0,05), тригліцеридів (R=-0,45, p<0,05), діастолічного артеріального тиску (R=-0,54, p<0,05). Високий рівень маркерів запалення, ендотеліальна дисфункція та зміни кардіальної гемодинаміки частіше визначалися в пацієнтів з постінфарктною СН старшої вікової групи.

Heart failure (HF) is a major cause of morbidity and mortality. Its incidence is increasing, in part because of the growing number of myocardial infarction survivor patients and due to advances in drug therapy and cardiovascular interventions [23]. After myocardial infarction, physiological and anatomical ventricular changes occur. Left ventricular dilatation, eccentric hypertrophy, thinning of myocardial wall in the area of the scar and eventually left ventricular geometry alteration are aspects that define this process [13].

These changes are collectively known as ventricular remodelling, and they start after the myocardial infarction (even before appearance of some symptoms) as a progressive process that involves a worse prognosis for patients [25].

There is also an inflammatory reaction with release of cytokines, growth factors and production of reactive forms of oxygen [20], which contributes to perpetuate ventricular dysfunction.

Myocardial infarction triggers an intense inflammatory response that is essential for cardiac repair, but which is also implicated in the pathogenesis of post infarction remodelling and heart failure. Signals in the infarcted myocardium activate toll-like receptor signalling, while complement activation and generation of reactive forms of oxygen induce cytokine and chemokine upregulation. Leukocytes recruited to the infarcted area, remove dead cells and matrix debris by phagocytosis, while preparing the area for scar formation [12].

In addition to the traditional risk factors of age, lipid levels, diabetes, hypertension, and smoking, a number of risk markers are now available for improving the evaluation of the post–myocardial infarction patient. These include left ventricular function, angiographic findings, peak creatine kinase or troponin levels, and B-type natriuretic peptide. C-reactive protein is an emerging risk marker that is recommended to complement the assessment of patients at primary cardiovascular risk and, to a more limited extent, stable patients at secondary risk [15].

It is now believed that C-reactive protein recognizes and binds phosphorylcholine molecule to microorganisms and also oxidizes low-density lipoproteins (LDL) and apoptotic cells. It interacts with complement to form the membrane attack complex and triggers proinflammatory signals to activate the immune system, which is helpful in bacterial infections, but may be maladaptive in the presence of excessive oxidized LDL or tissue damage. High levels in the presence of oxidized LDL accelerate atherosclerosis (promoting uptake of LDL by macrophages and facilitating foam cell formation) and augment inflammation within plaque, often leading to rupture and thrombotic vascular occlusion.

Several trials have demonstrated a high predictive value of C-reactive protein in stable and unstable angina, irrespective of troponin [14] and atherosclerosis development [21].

Endothelial dysfunction is related to HF initiation and progression and is associated with adverse outcomes in those with symptomatic and asymptomatic LV dysfunction [2, 6] and in acute and chronic HF [1, 10]. The degree of endothelial dysfunction correlates with HF severity and functional capacity [17]. Endothelial dysfunction independently predicts major clinical events in HF [10], including mortality risk [18, 24]. In patients with and without coronary artery disease, presence of epicardial or microvascular endothelial dysfunction predicts death [4, 19]. Endothelial dysfunction is also associated with HF risk factors (e.g., hypertension, diabetes) [3, 9].

Preservation of endothelial function in HF is associated with improved LV function [1], and recovery is related to improved outcome [22]. In HF, impaired flow-mediated dilatation (FMD) of the brachial artery is common and is associated with poor outcomes irrespective of etiology [17, 18, 24]. Abnormal FMD predicts incident cardiovascular events in older adults, a population that has a lower FMD and is also often at increased HF risk [7]. Impaired brachial artery FMD.

MATERIALS AND METHODS

Baseline Study

The study was conducted with approval from the Ethics committee at State Establishment «Dnipropetrovsk medical academy of Health Ministry of Ukraine» according to principles outlined in the Helsinki declaration.

Patients (n=45) aged 40 to 80 years, 33 males and 12 females with diagnosed CHF with preserved ejection fraction with chronic heart failure (HFpEF), according to ESC guidelines (2012) [11], and their functional class according to NYHA classification for HF were included. All patients got standard treatment for HF according to ESC guidelines 2012 [11].

Patients with recent acute myocardial infarction (< 6 months), ejection fraction (EF) ≤45, 2nd and 3rd degree heart block, diabetes mellitus (DM) glycated haemoglobin ≥7, acute, chronic renal and hepatic failure were excluded.

Groups of patients were comparable in age, gender structure, BMI, blood pressure, heart rate, glucose, lipid spectrum and treatment (table 1).

Standard laboratory blood tests for erythrocyte sedimentation rate, haematological parameters, lipid profile, glucose, renal and liver function tests were performed and body mass index(BMI) for all patients was calculated.

Echocardiographic examination was made with «VIVID 3», GE Medical Systems - USA in B, M, 2D, CFM, PW - mode pulse sensor 3S (3,5 MHz). Brachial artery measurements: the methods used to measure the BA diameter, determining % FMD and obtain baseline and hyperemic BA flow velocities and derive the respective flow volumes have been previously described [5, 8]. Calculation of FMD: In calculation of FMD as a percentage the peak diameter in response to reactive hyperemia in relation to the baseline diameter changes, FMD is expressed as a percent change in vessel caliber [16].

Study design:

We divided all patients into two main groups. 1st group: 25 patients with HFpEF and history of myocardial infarction. 2nd group: 20 patients with HFpEF and stable angina (without myocardial infarction in anamnesis).

Aim of our study – to evaluate the level of inflammatory markers (white blood cells and C-reactive protein), endothelial function and cardiac hemodynamic in different age patients with post infarction heart failure.

Statistical analysis:

In order to accomplish the analysis of data, we used statistical program V.6.1 (Stat Soft inc), and ‹Excel 2013› Microsoft. Data are shown as a number of subjects (%) or median [interquartile range (IQR) because data are not normal distribution. The Mann-Whitney U-test and Wilcoxon test were used to analyze differences between two independent and dependent samplings respectively. Correlation coefficient Spearman (R) was calculated. A p value <0.05 was considered statistically significant.

RESULTS AND DISCUSSION

Demographic, clinical and analytic characteristics of patients were summarized in table 1.

There were not any significant differences in blood glucose level, heart rate, cholesterol, triglyceride and in systolic, diastolic blood pressure.

More males than females had post infarction heart failure, while stable angina was prevalent more in females. The predominant risk factor was arterial hypertension with a more severe clinical course in patients with MI in anamnesis, 92% of them with 3rd stage, while 70% of patients with stable angina – with 2nd stage arterial hypertension. 82% of patients have 3rd functional class heart failure (NYHA classification), while 18 % of them with 2nd functional class.

Based on the results of a doppler echocardiography in patients with HFpEF, the median LVEF was 57 [46.5; 65]%. Analyzing the state of cardiac hemodynamics in these patients, there was no significant difference between the ejection fraction level, left ventricle end diastolic dimension, left atrium size, pulmonary artery pressure between pts groups ($p>0.05$). At the same time, patients with a history of myocardial infarction had significantly higher levels of left ventricle end diastolic volume, left ventricle end systolic dimension ($p<0.05$). There was revealed direct correlation between LVEDV, LVESD and age - $R=0.68$ ($p<0.05$), $R=0.52$ ($p<0.05$). Further analysis of cardiac hemodynamics depending on age revealed significant differences between LVEDV indices in patients with myocardial infarction ($p<0.05$). In patients with MI older than 60 years, a significantly higher LVEDV, LVESD, and lower ejection fraction ($p<0.05$) were noted. These differences characterize the processes of post infarction remodeling of the myocardium, which were more significant in patients of the elderly contingent.

Analyzing the indices of inflammation in patients with HFpEF, the median level of blood leukocytes was 6.7 [5.6; 7.9] x 10^9, while the rate was within the norm in all patients. A significantly higher level of leukocytes was found in patients with HFpEF with a history of myocardial infarction, in both groups ($p<0.05$) (Fig. 1). A direct correlation between the leukocyte count and age in patients with HFpEF-R = 0.48 ($p<0.05$) was also found.

The median level of the CRP in the examined patients was 4.7 [2.5; 7.1] mmol / l. A moderate increasing of the CRP level was noted in 5 (11.1%) patients with HFpEF. Patients with HFpEF with a history of myocardial infarction had a significantly higher level of CRP, age aspect including ($p<0.05$)

(Fig.). A direct correlation between CRP level and age was established in patients with HFpEF-R=0.46 ($p<0.05$). The obtained results characterize a significantly higher level of inflammation markers in patients with HFpEF on the background of a previous myocardial infarction.

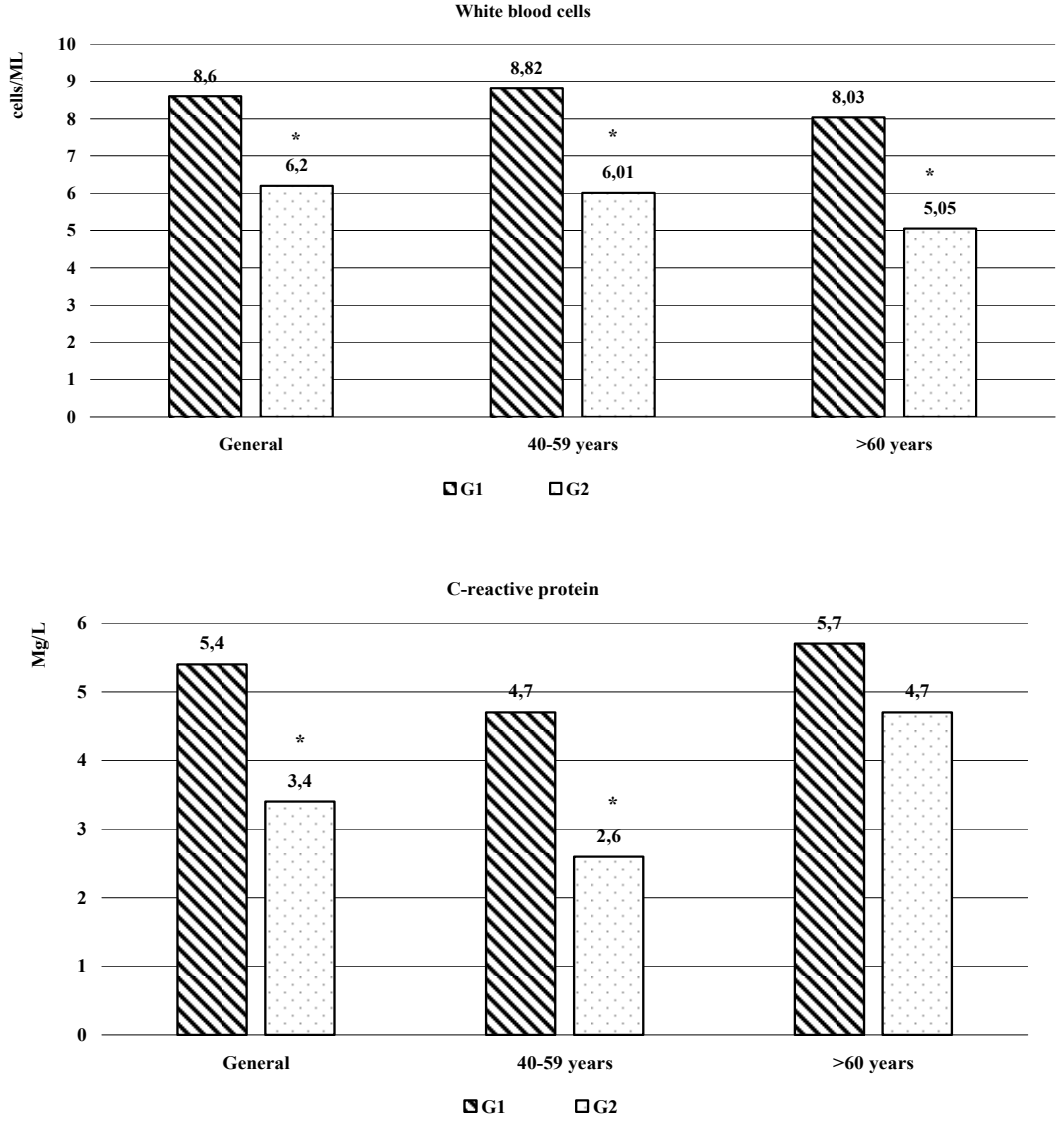
Table 1

Baseline characteristics of the study population

Characteristics		1st group Post infarction CHF (n=25)	2ndgroup CHF with Stable angina in anamnesis (n=20)
Gender	Males (%)	21 (84)	12 (60)
	Females (%)	4 (16)	8 (40)
Age, years		66 [57; 77]	68,5 [66; 70,3]
Heart rate, beat/minute		72,5 [68,5; 78]	77 [73; 79,5]
Systolic blood pressure, mm Hg		135 [121,3; 157,5]	137,5 [131,3; 140]
Diastolic blood pressure, mm Hg		80 [78,4; 90]	82,5 [80; 96,3]
Arterial hypertension, %		20 (80%)	12(60%)
BMI		28,4 [25,6; 29,9]	31,6 [27,3; 31,6]
Blood glucose, mmol/l		5,3 [5; 5,5]	5,2 [4,9; 5,3]
Cholesterol, mmol/l		4,7 [3,9; 5,7]	4,5 [4,2; 4,7]
Triglycerides, mmol/l		1,2 [1,1; 2,0]	1,2 [0,9; 1,4]
Treatment history, no. (%)			
Beta-blocker		16 (64)	10 (50)
Angiotensin converting enzyme inhibitor		10 (40)	6 (30)
Aldosterone receptor inhibitor		7 (28)	3 (15)
Statins		21 (84)	14 (70)

FMD median in patients with HFpEF was 4.6 [0.3; 14,5]%, endothelial dysfunction was noted in the majority of patients – 33 (73.3%). The level of FMD in all age groups had significant differences, the lowest level was observed in the group of patients older than 60 with myocardial infarction ($p<0.05$) (table 2). Vasoconstriction and the absence of FMD dynamics during a test with reactive hyperemia were recorded in 8 (17.8%) patients. Among patients with HFpEF and myocardial infarction in anamnesis, there were patients with reliably more frequent signs of endothelial dysfunction ($p <0.05$) as compared with group 2.

It was revealed that in the older age group with myocardial infarction the signs of endothelial dysfunction ($p<0.05$) are manifested significantly more frequently (table 3). The inverse correlation between the levels of FMD and CRP ($R= -0.48$, $p<0.05$), triglycerides ($R= -0.45$, $p<0.05$), diastolic blood pressure ($R= -0.54$, $p<0.05$) was established.



* - p- significant differences between 1 and 2 groups

Inflammatory markers changes

Thus, patients with HFpEF and myocardial infarction in anamnesis were characterized by significantly higher levels of markers of inflammation, endothelial dysfunction, hemodynamic changes. In this case, the most pronounced violations of these indicators were observed in patients older than 60 years.

Table 2

Endothelial function indicators in pts HFpEF

	1st group	2nd group
Baseline brachial artery diameter (D1)	**4,6 [4,3; 5,2]**	**4,5 [4,3; 5,2]**
Hypermic brachial artery diameter (D2)	**4,8 [4,6; 5,3]**	**4,8 [4,5; 5,3]**
Flow-mediated dilatation (FMD), %	**2,1 [0,5; 16,2]**	**5,4 [0,6; 9,7]***
Pts with estimated endothelial dysfunction, n (%)	**21 (84)**	**12 (60)***

Notes: * - p- significant differences between 1 and 2 groups

Table 3

Endothelial function indicators in HFpEF pts according to age difference

	1st group n=25		2nd group n=20	
	40-59 y.o n = 11	≥ 60 y.o n = 14	40-59 y.o n = 10	≥ 60 y.o n = 10
Baseline brachial artery diameter (D1)	**5,0 [4,6; 5,5]**	**4,6 [4,3; 5,1]**	**4,8 [4,6; 5,5]**	**4,5 [4,5; 5,2]**
Hypermic brachial artery diameter (D2)	**5,4 [4,9; 5,6]**	**4,9 [4,5; 5,3]**	**4,9 [4,8; 5,4]**	**4,8 [4,8; 5,2]**
Flow-mediated dilatation (FMD) %	**3,3 [1,8; 16,7]**	**2,4 [-1,6; 9,7]***	**6,2 [3,5; 23,2]#**	**4,4 [0,5; 15,8]*#**
Pts with estimated endothelial dysfunction, n (%)	**9 (81,8)**	**12 (85,7)**	**4 (40)#**	**8 (70)**

Notes: * - p- significant differences between 40-59 y.o and ≥60 y.o groups, # - p- significant differences between 1 and 2 groups

CONCLUSION

1. Significantly high levels of inflammation markers (CRP & WBCs) in patients with HFpEF and myocardial infarction in anamnesis, especially elderly patients were established.
2. Endothelial dysfunction was noted in the majority of patients in both groups, the worst endothelial function (endothelial dysfunction) was observed in patients older than 60 with history of myocardial infarction.
3. Marked cardiac hemodynamic changes were observed in elderly patients (≥60 years old) with HFpEF and myocardial infarction in anamnesis.

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